6. A method of importing a biologically active molecule into a cell in a subject comprising administering to the subject a complex comprising the molecule linked to [an] a mammalian hydrophobic importation competent signal peptide, thereby importing the molecule into the cell of the subject,

wherein said cell is selected from a tissue cell or an organ cell;

wherein said biologically active molecule is selected from the group consisting of:

(i) a protein or a portion of a protein selected from the group consisting of a growth factor polypeptide, an enzyme polypeptide, a transcription factor polypeptide, a toxin polypeptide, an antigenic polypeptide, a vaccine polypeptide, an antibody polypeptide;

(ii) a portion of a nucleic acid selected from the group consisting of a plasmid DNA, a DNA coding sequence, an mRNA and an antisense RNA;

(iii) a carbohydrate; a lipid; a glycolipid;

wherein said tissue cell or organ cell is further selected from the group consisting of: an immune system cell, a blood vessel cell, a lung epithelium cell, a kidney cell, a fibroblast cell, an epithelial cell, an endothelial cell, a tumor cell, a lymphocyte, an antigen presenting cell, a T cell and a Schwann cell; and,

wherein said complex induces or inhibits a biological response in the cell that is selected from the group consisting of: a mitogenic response in the cell, an inhibition of cell division in the cell, an immune antibody or cytokine response in the cell, an inhibition of an autoreactive immune response in the cell, an inhibition of transcription in the cell, an inhibition of tyrosine phosphorylation in the cell and an inhibition of nuclear translocation of a transcription factor complex from the cytosol to the nucleus in the cell.

7. The method of Claim 6, wherein the molecule is selected from the group consisting of a peptide, polypeptide, and protein.

8. The method of Claim 6, wherein the molecule is selected from the group consisting of a nucleic acid, carbohydrate, lipid, and a glycolipid [and therapeutic agent].

9. The method of Claim 6, wherein the signal peptide comprises the amino acid sequence set forth in SEQ ID NO:5.

10. The method of Claim 6, wherein the molecule is an antigenic peptide.

11. A method of importing a biologically active molecule into the nucleus of a cell in a subject comprising administering to the subject a complex comprising the molecule linked to an importation competent signal peptide and a nuclear localization peptide, thereby importing the molecule into the nucleus of the cell of the subject.

12. The method of Claim 11, wherein the signal peptide comprises the amino acid sequence set forth in SEQ ID NO:5.

13. The method of Claim 11, wherein the nuclear localization peptide comprises the amino acid sequence set forth in SEQ ID NO:2.

14. The method of Claim 11, wherein the nuclear localization peptide comprises the amino acid sequence set forth in SEQ ID NO:10.

15. The method of Claim 11, wherein the nuclear localization peptide comprises the amino acid sequence set forth in SEQ ID NO:11.

16. A method of regulating the growth of a cell in a subject comprising administering to the subject [a]the complex of claim 1 comprising a growth regulatory peptide linked to [an]the importation competent signal peptide[, thereby regulating the growth of the cell in the subject].

17. The method of Claim 16, wherein the cell is a tumor cell.

18. The method of Claim 16, wherein the growth regulatory peptide stimulates the cell growth and comprises the nuclear localization sequence of acidic fibroblast growth factor.

19. The method of Claim 18, wherein the growth regulatory peptide comprises the amino acid sequence set forth in SEQ ID NO:3.

20. The method of Claim 18, wherein the growth regulatory peptide comprises the amino acid sequence set forth in SEQ ID NO:4.

21. The method of Claim 16, wherein the growth regulatory peptide inhibits the cell growth.

22. The method of Claim 21, wherein the growth regulatory peptide comprises the amino acid sequence set forth in SEQ ID NO:9.

23. A method of inhibiting expression in a cell in a subject of a gene controlled by transcription factor NF-κB comprising administering to the subject [a]the complex of claim 1 comprising an importation competent signal peptide linked to a nuclear localization peptide of an active subunit of NF-κB complex.

24. The method of Claim 23, wherein the subunit of NF-κB is subunit p50.

25. The method of Claim 24, wherein the complex comprises the amino acid sequence set forth in SEQ ID NO:9.

26. A method of stimulating the immune system of a subject comprising administering to the subject [a]the complex of claim 1 further comprising an importation competent signal peptide linked to an antigenic peptide.

33. A method of screening signal peptides for the ability to effect the importation of a biologically active molecule into a cell comprising administering to the cell a complex comprising

the molecule linked to the signal peptide and determining whether the molecule is imported into the cell, the presence of importation of the molecule indicating a signal peptide which can effect importation.

PLEASE ENTER NEW CLAIMS 34-38 as follows: namely,

34. The method of claim 6, wherein said complex further comprises a peptide therapeutic drug agent for treating a disease selected from the group consisting of: a heart condition, a cancer, an endocrine disorder, a neurological defect, a respiratory condition, an allergy and an autoimmune disease.

35. The method of claim 6, wherein said biological response is inhibition of transcription in the cell.

36. The method of claim 35, wherein said biological response is altered expression of a cytokine, a growth factor, an interleukin, a colony stimulating factor, a plasminogen activator, a procoagulant tissue factor and a virus gene product.

37. The method of claim 36, wherein said interleukin is IL-1, TNF-α or IL-6.

38. The method of claim 36, wherein said virus gene product is an HIV or a CMV gene product.

(ii) REMARKS

Support for the Amendments:

Support for the amendments to the claims is found throughout the specification. Particular support for the amendment to claim 1 is found, e.g., at page 6, lines 21-27; at page 14, lines 13-21; at page 16, line 25, through page 17, line 28, and at page 18, line 9. Particular support for new claim 34 is found, e.g., at page 1, lines 24-27, and particular support for new claims 35-38 is found, e.g., at page 16, line 25, through page. 17, line 3.

Information Disclosure Statement:

The citation of "Delli-Bovi et al., Cell 50:3206-3142" in the Information Disclosure Statement filed April 6, 2000 was apparently in error, as Applicants have been unable to identify a scientific reference corresponding to this citation. Applicants apologize for any inconvenience caused to the Examiner as a result of this error.

Drawings:

Corrected drawings will be provided when there is allowable subject matter.

Rejections Under 35 USC § 112, First Paragraph - Enablement:

Claims 6-15 stand rejected under 35 USC § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to "make and/or use" the invention, it being asserted that an *In re. Wands* analysis supports this rejection. This assertion is respectfully traversed. Further, as follows, neither "very broad" claims nor "gene therapy" are recognized as a basis for an enablement rejection, or alternatively, a rejection based in a lack of operability or utility, i.e., 35 USC 101. The position of the Office is set forth as follows: namely,

> "The present claims are **very broad**. Claim 6 encompasses a method of importing any biologically active molecule into any cell in a subject by administering a complex comprising the molecule linked, covalently or non-covalently, to any importation competent signal peptide. Claim 11 encompasses a method of importing any biologically active molecule into the nucleus of any cell in a subject by administering a complex comprising the molecule linked, covalently or non-covalently, to any importation competent signal peptide and a nuclear localization peptide.
> The nature of the invention is a method of importing a biologically active molecule into a cell or a cell nucleus of a subject. The only use disclosed in the specification for this method is as a method of treatment. See for instance p. 1, lines 19-20 and 24, p. 3, lines 9-17 and p. 19, line 10-p.20, line 7. The biologically active molecule may be a nucleic acid (see also p. 19, lines 7-17). Delivery of a nucleic acid to a cell in vivo for therapeutic purposes is gene therapy. Therefore, the claims encompass gene therapy.
> An analysis of the prior art as of the **effective filing date**" {emphasis added} "of the present application shows the complete lack of documented success for any treatment based on gene therapy."

Priority - Applicants respectively submit that the present application is a divisional of serial number 09/170,754 (now USPN 6,043,339), which was filed October 13, 1998 as a divisional of 09/052,784 (now abandoned), filed March 31, 1998 as a continuation of 08/258,852 (now USPN 5,807,746) which was filed June 13, 1994. The claimed invention has, in different aspects, now been under continuous examination for more than eight years and priority is claimed, for purposes of prior art and inventive genius, to June 13, 1994.

The Claimed Invention - Applicant's claimed invention is a method of treating a cell, not limited to gene therapy. For purposes of 35 U.S.C.§ 112, first paragraph it is sufficient that one skilled in the art be able to make and use the invention for any purpose, i.e., there is not a requirement that a method function for all purposes; and, for purposes of 35 U.S.C. § 101 a lack of operability is overcome by any one credible utility for a claimed invention. The burden placed on the Office in establishing a *prima facie* showing is set forth in the Manual of Patent Examination Procedures at 706.03(a)(1)(2)(a), i.e.,

> "If the applicant has asserted that the claimed invention is useful for any particular purpose (i.e., a "specific utility") and that assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility. Credibility is to be assessed from the perspective of one of ordinary skill in the art in view of any evidence of record (e.g., data, statements, opinions, references, etc.) that is relevant to the applicant's assertions. An applicant must provide only one credible assertion of specific utility for any claimed invention to satisfy the utility requirement.

Credible Treatment vs. "Cure" - Applicants traverse the Office characterization of the gene therapy prior art, or its direct relevance to the 'claimed invention' presently under examination, or that the art relied upon teaches "*..the complete lack of documented success for any treatment based on gene therapy.*"

The art relied upon by the Office in forming basis for the rejections does not support a *prima facie* showing of lack of credible utility, e.g. consider the following: namely,

> "The first clinical protocol for gene therapy was carried out in 1990 when a patient with severe combined immunodeficiency syndrome (SCID) underwent ex vivo transduction of peripheral T lymphocytes with a murine leukemia retroviral vector (MLV) carrying the adenosine deaminase (ADA) gene. Tests conducted three years later showed that more than 30% of circulating T cells of the patient contained the transduced gene with a significant improvement of the immune competence (Blaese et al., 1995). To date this is the first well-characterized example of a gene transfer leading to some benefit for the patient's health." (Document W, Palu et al., page 1, right column, line 4 to page 2, left column, line 7);
>
> "An example where limited transduction could sustain a therapeutic benefit is the case of hemophilia B, disease caused by the deficiency of the blood clotting protein called factor IX. Five percent of the normal circulating levels of this protein have been shown to be sufficient to improve substantially the quality of life of the affected patients." (Document W, Palu et al., page 2, left column, lines 20-27);
>
> "We also need to consider how much of the therapeutic protein should be delivered. In haemophilia B, which is caused by a deficiency of a blood-clotting protein called factor IX, giving patients just 5%of the normal circulating levels of this protein can substantially improve their quality of life. Most people have about 5 μg of factor IX per millilitre of plasma, produced by the 10^{13} cells that make up the liver. So we need to deliver a correcting gene to 5 x 10^{11} cells - that is 5% of liver cells. Alternatively, fewer liver cells would need to be modified if more factor IX could be produced per cell, without being deleterious. In the brain, however, gene transfer to just a few hundred cells could considerably benefit patients with neurological disease." (Document U, Verma et al., page 239, middle column, line 2 through right column, line 2); and,
>
> "Over the past 30 years, DNA delivery, especially via the nonviral route (i.e., transduction), has become a powerful and popular research tool for elucidating gene structure, regulation, and function. Indeed, a recent search of the keyword "transfection" using the National Center for Biotechnology Information's (NCBI; Rockville, MD) MEDLINE database (www.ncbi.nlm.nig.gov/PubMed/) yielded more than 50,000 papers. DNA delivery has also been pivotala in developing new approaches (e.g., gene therapy and DNA vaccination) for treating and controlling diseases that are likely to impact clinical medicine and biotechnology over the next few years. Before such applications can be realized, however, the relative inefficiency and cytotoxicity of modern synthetic DNA delivery systems must be addressed." (Document V, Luo et al., page 33, first paragraph of the introduction, left column.)

The documents relied upon, thus, do not provide the requisite *prime facie* showing for a lack of credible use for the claimed invention, i.e., even in gene therapy. To date, there exists no codified Federal requirement that a therapeutic agent, including a gene therapy, must successfully cure a hereditable genetic disease to be considered 'therapeutic', or to be approved by the FDA. It is well known that most pharmaceutical agents presently in use only transiently alleviate symptoms of a disease activity and most often, not in 100% of patients. The US PTO is not directed to determine drug efficacy. The 35 USC § 112 enablement requirement is that one skilled in the art be able to practice the invention. The enablement requirement is not based in FDA codes insuring safety and efficacy of active pharmaceutical ingredients. It has been posited previously, that there is also no advantage to the public in a requirement that new and potentially useful therapeutic advances be submitted to clinical trials before claims should be allowed.

Instead, such an approached as been viewed as detrimental to the public good since it may delay development of new therapies.

Guidance - In order to satisfy the enablement requirement of 35 U.S.C. § 112, first paragraph, the specification must teach one skilled in the art to make and use the invention without undue experimentation. Atlas Powder Co. v. E.I. DuPont de Nemours, 750 F.2d 1569, 224 USPQ 409. This requirement can be satisfied by providing sufficient disclosure, either through illustrative examples or terminology, to teach one of skill in the art how to make and how to use the claimed subject matter without undue experimentation. This clause does not require "a specific example of everything within the scope of a broad claim." In re Anderson, 176 USPQ 331, at 333 (CCPA 1973). Rather, the requirements of §112, first paragraph "can be fulfilled by the use of illustrative examples or by broad terminology." In re Marzocchi et al., 469 USPQ 367 (CCPA 1971).

Further, because "it is manifestly impracticable for an applicant who discloses a generic invention to give an example of every species falling within it, or even to name every such species, it is sufficient if the disclosure teaches those skilled in the art what the invention is and how to practice it." In re. Grimme, Keil and Schmitz, 124 USPQ 449, 502 (CCPA 1960). Thus, there is no doubt in law that a patentee's invention may be broader than the particular embodiments shown in the specification. A patentee is not only entitled to narrow claims, particularly directed to the preferred embodiment, but also to broad claims that define the invention without a reference to a specific instrumentalities. Smith v. Snow, 294 U.S. 1, 11, 24 USPQ 26, 30 (1935).

There is also no requirement for disclosure of every species within a genus. Applicant is entitled to claims that are commensurate in scope not only with what applicant has specifically exemplified, but commensurate in scope with that which one of skill in the art could obtain by virtue of that which the applicant has disclosed. The inquiry with respect to scope of enablement under 35 U.S.C. § 112, first paragraph, is whether it would require undue experimentation to make and use the claimed invention. A considerable amount of experimentation is permissible, particularly if it is routine experimentation. The amount of experimentation that is permissible depends upon a number of factors, which include: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, and the breadth of the claims. Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int'f. 1986); see also In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988).

In consideration of documents possibly relevant in an *In re. Wands* evaluation, submitted herein is provided the Declaration under 35 U.S.C. § 132 of John S. Sundsmo, Ph.D. describing how a routine keyword search was conducted of the scientific literature indexed and available at the Internet Website for

the National Library of Medicine to identify documents published by Dr. J.J. Hawiger, an inventor in the instant application, as well as, "Related Articles, Links".

35 U.S.C. § 112, First Paragraph - "*The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.*"

***In re. Wands* Inquiry:**

A. Undue Experimentation is Not Required To Make and Use

Methods known to those of skill in the art for "the manner and process of making and using" the claimed method of the invention include: for example,

1. Mixing - Those skilled in the art would generally acknowledge that ***mixing*** was of ordinary skill in the art at the time the priority application was filed, i.e., mixing together into a solution: an oligonucleotide or plasmid DNA and "..a complex comprising a biologically active molecule linked to an importation competent signal peptide" (Claim 6) or "..a complex comprising the molecule linked to an importation competent signal peptide and a nuclear localization peptide" (Claim 11). That such a mixed solution is sufficient, has been illustrated e.g. after the filing date of the priority application as follows: namely,

Document AA, Morris et al. 1997, (Appendix A) confirms that an electrostatic complex is formed between an MPG peptide, i.e., containing both an importation competent signal peptide and a nuclear localization peptide, and an oligonucleotide when these components are mixed together. The complex reported effectively delivered the oligonucleotide, i.e., a biologically active molecule, into cells;

Document AB, Morris et al. 1999, (Appendix A) confirms that mixing together the MPG peptide of Document AA with a plasmid nucleic acid, i.e., a biologically active molecule, resulted in delivery of the plasmid into the cell and expression of the plasmid in the cell;

Document AC, Morris et al. 2000, (Appendix A), entitled "Translocating peptides and proteins and their use for gene delivery" reviewed the uses of importation competent signal peptides and nuclear localization peptides for delivery of genes into cells; and,

Document AD, Morris et al. 1999, (Appendix A) confirmed that passive complex formation between an importation competent peptide, (i.e., the MPG of Documents AA, AB and AC), and a biologically active peptide, (i.e., by mixing and then separating the resultant complexes), was also effective in promoting delivery of peptides, (i.e., instead of oligonucleotides), into cells.

2. Coupling - Those skilled in the art would generally acknowledge that ***coupling*** e.g. of peptides to peptides, peptides to proteins, peptides to oligonucleotides and peptides to plasmids was of ordinary skill in the art at the time the priority application was filed: for instance,

> **Document AE** at page 295, 1994 Sigma Chemical catalogue, lists 39 different "Cross-Linking Reagents";
>
> **Document AF**, Rojas et al. 1998, confirmed that coupling an importation competent peptide, (i.e., referred to as a membrane translocation signal, MTS), to a protein was effective to transport a polypeptide having an apparent molecular mass of 41-kDa.

3. Peptide Synthesis - Those skilled in the art would generally acknowledge that ***peptide synthesis*** was of ordinary skill in the art at the time the invention was made, i.e., to synthesize an importation competent peptide: for instance,

> **Document AG**, 22nd Edition of "Harper's Biochemistry published in 93-94, (Appendix A) contained instructions that peptide so synthesized were useful ".. not only for confirming de novo synthesis of the primary structures of proteins, but for immunology, for producing vaccines and polypeptide hormones, and conceivably also for treating selected inborn errors of metabolism." (page 38, right column, last paragraph before "References".)

4. Clinical Delivery, Dosing and Formulation of Protein and Peptide-Based API - Protein and/or peptide-based active pharmaceutical ingredients (API) approved for use in humans and animals by the United States FDA and USDA, as well as, by International regulatory authorities, are multiple and include at least products in the following many different illustrative general product classes: e.g.,

> hormones (e.g., insulin, estrogen, progestin, ACTH, GnRH, thyroid hormone, vassopressin and the like); growth factors (e.g., growth hormone, erythropoietin, GM-CSF, G-CSF and the like); angiotensin converting enzyme (ACE) inhibitors; anti-infective agents (e.g. peptide antibiotics); nutritional perenteral amino acids and peptide combinations; enzymes (e.g. DNase); biological response modifiers (e.g., IL-2, α-interferon, β-interferon and the like); immune globulins (e.g., anti-toxins and the like); anti-neoplastic agents (e.g., monoclonal antibodies and the like); toxoids and vaccines (e.g., diphtheria, tetanus, smallpox, polio and influenza vaccines); neurotoxins (e.g., BOTOX, Curare and the like); collagen (injectable, resorptive surgical sponges, wound dressings, dental implants and the like); coagulation factors (e.g., thrombin, Protein C, Factors V, VIII, IX, X, VWF and the like); and, anti-fibrinolytic agents (urokinase, tissue plasminogen activator, streptokinase and the like).

API such as these have been routinely developed and administered since at least the 1930s (e.g., insulin) and after 6-7 decades of clinical use the surrounding clinical and pharmaceutical arts may by now be considered relatively mature.

B. The Level of Skill in the Art is High

As the Examiner has correctly observed at page 6 of Paper No. 15, line 5: "*The relative skill of those in the art of gene therapy is high.*" In addition, the relative skill of those in the clinical arts delivering protein- and peptide-based therapies to humans is high.

Absolute predictability is not a statutory requirement under 35 U.S.C. § 112, and instead, it is sufficient that the invention be enabling to the extent that it places the invention in the possession of the public. Human clinical trials and market forces will ultimately determine whether therapeutic approaches are viable.

C. Teaching and Guidance in the Specification

Applicants teach illustrative complexes formed between importation competent peptides and biologically active molecules as follows: namely,

1. Illustrative known therapeutic uses of biologically active peptides were disclosed by Applicants as follows: namely,

" Peptides have been developed for many therapeutic uses. For example, diseases currently targeted by new peptide drugs include heart conditions, cancers, endocrine disorders, neurological defects, respiratory conditions, allergies and autoimmune diseases. Although the manufacture of known therapeutic peptides can be achieved by known methods, i.e., classic synthetic techniques or recombinant genetic engineering, delivery of the peptides into a cell has remained problematic, since they cannot readily cross biological membranes to enter cells." (page 1, lines 24-31).

2. Illustrative coupling and construction methods forming complexes useful in the methods of the invention were set forth in 1994 as follows: namely,

"By "linked" as used herein is meant that the biologically active molecule is associated with the signal peptide in such a manner that when the signal peptide crosses the cell membrane, the molecule is also imported across the cell membrane. Examples of such means of linking include (1) when the molecule is a peptide, the signal peptide (and a nuclear localization peptide, if desired) can be linked by a peptide bond, i.e., the two peptides can be synthesized contiguously; (2) when the molecule is a polypeptide or a protein (including antibody), the signal peptide (and a nuclear localization peptide, if desired) can be linked to the molecule by a peptide bond or by a non-peptide covalent bond (such as conjugating a signal peptide to a protein with a crosslinking reagent); (3) ***for molecules that have a negative charge, such as nucleic acids, the molecule and the signal peptide (and a nuclear localization peptide, if desired) can be joined by charge-association between the negatively-charged molecule and the positively-charged amino acids in the*** peptide or by other types of association between nucleic acids and amino acids; (4) chemical ligation methods can be employed to create a covalent bond between the carboxy-terminal amino acid of the signal peptide (and a nuclear localization peptide, if desired) and the molecule. Methods (1) and (2) are typically preferred." (The specification as filed in 1994, page 12, line 15 - page 13, line 2; emphasis added);

"Examples of method (1) are shown below wherein a peptide is synthesized, by standard means known in the art,[24,25] that contains, in linear order from the amino-terminal end, a signal peptide sequence, an optional spacer amino acid region, and a biologically active amino acid sequence. Such a peptide could also be produced

through recombinant DNA techniques, expressed from a recombinant construct encoding the above-described amino acids to create the peptide.[28]" (page 13, lines 4-10);

"For method (2), either a peptide bond, as above, can be utilized or a non-peptide covalent bond can be used to link the signal peptide with the biologically active polypeptide or protein. This non-peptide covalent bond can be formed by methods standard in the art, such as by conjugating the signal peptide to the polypeptide or protein via a crosslinking reagent, for example, glutaraldehyde. Such methods are standard in the art.[29] For method (3) the molecules can simply be mixed with the signal peptide and thus allowed to associate. These methods are performed in the same manner as association of nucleic acids with cationic liposomes.[32-34] Alternatively, covalent (thioester) bonds can be formed between mucleic acids and peptides. Such methods are standard in the art." (page 13, lines 12-22);

"For method (4), standard chemical ligation methods, such as using chemical crosslinkers interacting with the carboxy-terminal amino acid of the signal peptide, can be utilized. Such methods are standard in the art (*see*, e.g., Goodfriend,[31] which uses water-soluble carbodiimide as a ligating reagent) and can readily be performed to link the carboxy terminal end of the signal peptide to any selected biologically active molecule." (page 13, lines 24-29).

3. Illustrative biologically active molecules useful according to the methods of the invention were set forth in 1994 as follows: namely,

" Examples of biologically active molecules include proteins, polypeptides and peptides, which include functional domains of biologically active molecules, such as growth factors, enzymes, transcription factors, toxins, antigenic peptides (as for vaccines), antibodies, and antibody fragments. Additional examples of biologically active molecules include nucleic acids, such as plasmids, coding DNA sequences, mRNAs and antisense RNA molecules, carbohydrates, lipids and glycolipids. Further examples of biologically active molecules include therapeutic agents, in particular those with a low cell membrane permeability. Some examples of these therapeutic agents include cancer drugs, such as Daunorubicin,[26] and toxic chemicals which, because of the lower dosage that can be administered by this method, can now be more safely administered." (The specification as filed in 1994, page 6, lines 21-32);

4. Illustrative dosage forms useful in the methods of the invention were set forth in 1994 as follows: namely,

"Depending on the intended mode of administration, the pharmaceutical compositions may be in the form of solid, semi-solid or liquid dosage forms, such as, for example, tablets, suppositories, pills, capsules, powders, liquids, suspensions, lotions, creams, gels, or the like, preferably in unit dosage form suitable for single administration of a precise dosage. The compositions will include, as noted above, an effective amount of the selected drug in combination with a pharmaceutically acceptable carrier and, in addition, may include other medicinal agents, pharmaceutical agents, carriers, adjuvants, diluents, etc." (page 9, line 28, through page 10, line 4)

5. Illustrative formulations useful in the methods of the invention were set forth in 1994 as follows: namely,

"For *in vivo* administration, the complex can be added to, for example, a blood sample or a tissue sample from the patient, or to a pharmaceutically acceptable carrier, e.g., saline and buffered saline, and administered by any of several means known in the art. Examples of administration include parenteral administration, e.g., by intravenous injection including regional perfusion through a blood vessel supplying the tissues(s) or organ(s) having the target cell(s), or by inhalation of an aerosol, subcutaneous or intramuscular injection, topical administration such as to skin wounds and lesions, direct transfection into, e.g., bone marrow cells prepared for

transplantation and subsequent transplantation into the subject, and direct transfection into an organ that is subsequently transplanted into the subject. Further administration methods include oral administration, particularly when the complex is encapsulated, or rectal administration, particularly when the complex is in suppository form." (page 8, lines 2-15); and,

"For solid compositions, conventional nontoxic solid carriers include, for example, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharin, talc, cellulose, glucose, sucrose, magnesium carbonate, and the like. Liquid pharmaceutically administrable compositions can, for example, be prepared by dissolving, dispersing, etc. an active compound as described herein and optional pharmaceutical adjuvants in an excipient, such as, for example, water, saline, aqueous dextrose, glycerol, ethanol, and the like, to thereby form a solution or suspension. If desired, the pharmaceutical composition to be administered may also contain minor amounts of nontoxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents and the like. Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see *Remington's Pharmaceutical Sciences*.[27]" (page 10, lines 6-18)

6. Illustrative routes of administration useful in the methods of the invention were set forth in 1994 as follows: namely,

"Parenteral administration, e.g., regional perfusion, if used, is generally characterized by injection. Injectables can be prepared in conventional forms, such as liquid solutions, suspensions, or emulsions. A slow release or sustained release system, such as disclosed in U.S. Patent No. 3,710,795, can also be used, allowing the maintenance of a constant level of dosage." (page 9, lines 22-26);

".. e.g., by intravenous injection including regional perfusion through a blood vessel supplying the tissues(s) or organ(s) having the target cell(s), or by inhalation of an aerosol, subcutaneous or intramuscular injection, topical administration such as to skin wounds and lesions, direct transfection into, e.g., bone marrow cells prepared for transplantation and subsequent transplantation into the subject, and direct transfection into an organ that is subsequently transplanted into the subject. Further administration methods include oral administration, particularly when the complex is encapsulated, or rectal administration, particularly when the complex is in suppository form." (page 8, lines 6-15)

"The complex can be administered to the subject by standard means known in the art for administering vaccines." (page 17, lines 31-32.

7. Contrary to the assertion of the Office, (i.e., at page 6, lines 13-20), that only cystic fibrosis treatments are enabled, illustrative treatment modalities useful according to the methods of the invention were set forth in 1994 as follows: namely,

" Furthermore, if known peptides for blocking autoreactive T cells are linked to a signal peptide and administered to a subject, an immunosuppressive effect can be stimulated in the subject. Such a method of stimulating immunosuppression can be used to treat autoimmune diseases such as multiple sclerosis." (page 18, lines 5-9);

"The present method, which provides an effective method for importing biologically active molecules into cells, has many uses, both *in vivo* and *ex vivo*. Specific utilities using the method are apparent and are exemplified as follows. *In vivo*, the method can be used to deliver into cells therapeutic molecules, such as peptides and proteins to regulate aberrant functions or to supply deficient cells; DNA for gene therapy (e.g., to provide the CFTR gene in cystic fibrosis patients); RNA for antisense therapy (e.g., to inhibit growth as in inhibiting expression in cancer cells); and therapeutic agents such as cancer drugs or toxic chemicals (which can be administered in lower dosages with this method as compared to previous methods not utilizing a signal peptide to more efficiently enter the cells). *Ex vivo*, the method allows efficient transfection of cells without

performing cell-damaging procedures. Therefore, this method is useful *ex vivo* in any method that utilizes transfection, such as transfecting reporter genes into cells to screen for compounds that affect expression of the reporter gene, and for transfecting bone marrow cells, blood cells, cells of an organ for subsequent transplantation into a subject, or culture cells, with a gene to effect protein expression in the cells." (page 19, lines 7-23);

"More specifically, this method can be used for anti-thrombotic therapy by administering functional domains of known cell receptors which mediate aggregation of platelets, by competitive binding. Additionally, the method can be used for immunosuppression in autoimmune diseases by introducing immunosuppressive peptides into cells involved in the immune response. Furthermore, growth inhibitors can be administered by this method to tumor cells to treat, for example, cancer cells." (page 19, lines 25-31); and,

"This method can also be used to facilitate the absorption of biologically active molecules from, e.g., the mouth, stomach or intestinal tract by facilitating movement of the molecules into the connective tissue beneath the lining of the digestive tract. Also, by allowing one to design signal peptides with modified amino acids, one can stabilize biologically active peptides by making them more resistant to peptidases and therefore also prolong the action of the peptide." (page 20, lines 1-7).

Applicants believe that they have met the burden requisite in 35 U.S.C. § 112, first paragraph. Contrary to the assertions of the Office that there is "no direction" and "no working examples", (page 6, line 17-page 7, line 2), Applicant's believe that their specification, combined with the state of knowledge in the therapeutic peptide arts was at the time of their invention, (and is now), sufficient to enable one skilled in the art, without undue experimentation, to construct a complex between an importation competent peptide and a biologically active molecule and determine whether the subject complex is suitable for use in a treating a cell in a subject according to the methods of the claimed invention, as demonstrated by the art over the past several years. As set forth further below, (i.e.., see :"Post-Filing Art" and "Commercialization" under Forman Analysis), several different importation competent peptide complexes have been successfully constructed; certain of those subject complexes have been tested in experimental animals; and, others are presently acknowledged to be in development as APIs by companies in the pharmaceutical and biotechnology industries.

Patents are written to enable those skilled in the art to practice the invention. A patent need not disclose what is well known in the art (W.L. Gore & Assoc. v. Gorlock, Inc., 721 F.2d 1540, 1556, 220 USPQ 303, 315).

D. Forman Analysis

The Office position is as follows: namely,

"The quantity of experimentation necessary to carry out the invention is high as the skilled artisan could not rely on the prior art or the present specification to teach how to use the claimed methods. In order to determine what effects exogenous transgene expression would have in any cell type, whether the effect could be exploited for treatment of a disease, how to deliver the given nucleic acid to the appropriate target cells with specificity

> and efficiency, and how to get sufficient expression to induce at least some therapeutic effect. With regard to all the other biologically active molecules claimed, one would have to determine how to direct/target the complex to the targeted cell type efficiently and whether a sufficient quantity of the complex is taken up by the target cell to achieve some therapeutic effect. Furthermore, since Applicant only speculates that all signal peptides will function as importation signal peptides, having demonstrated it only for Kaposi fibroblast growth factor, a skilled artisan will have to determine if any other known signal peptide can function as in" {sic/an} "importation signal. Since neither the prior art nor the specification provides the answers to all of these questions, it would require a large quantity of trial and error experimentally by the skilled artisan to do so." (page 7, lines 3-19).

Applicants traverse this characterization and provide the following guidance and post-filing art which has proven the utility of the claimed methods and exciting promising future therapeutic products currently under development in at least three different pharmaceutical and/or biotechnology companies.

Guidance - A considerable amount of experimentation is permissible, particularly if it is routine experimentation, i.e., construction of- and clinical administration of- therapeutic proteins and peptides including nucleic acid complexes prepared by mixing with importation competent peptides, supra. The amount of experimentation that is permissible depends upon a number of factors, which include: the quantity of experimentation necessary (supra), the amount of direction or guidance presented (supra), the presence of working examples (supra), the nature of the invention (supra), the state of the prior art (supra), the relative skill of those in the art (supra), the predictability of the art, and the breadth of the claims. Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int'f. 1986); see also In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988).

Copying - Post-filing art documents effectively rebut the position of the Office in regard to " ...sufficient expression to induce at least some therapeutic effect" and that that "...one would have to determine how to direct/target the complex to the targeted cell type efficiently and whether a sufficient quantity of the complex is taken up by the target cell to achieve some therapeutic effect." : namely,

1. For peptide complexes formed with peptide biologically active molecules, the following examples of copying are relevant for *in vivo* uses: namely,

a) Document AH, Hawiger and coworkers 2000, constructed an importation competent peptide, coupled it to a biologically active molecule, i.e., a cyclic nuclear localization signal, and as set forth in the instant application successfully used it to block nuclear localization of NFκB signaling complexes *in vivo* in a lethal murine septic shock animal model of inflammation (Appendix A, Supplemental Information Disclosure Statement). This is the same NFκB molecular target disclosed by Applicants/Hawiger in 1994 in the instant application;

b) Document AI, Xia et al. 2001, copied and confirmed expression of β-glucuronidase in the brains of mice following intravenous or intracerebral injection of importation competent peptide complexes formed with this biologically active molecule, i.e., an enzyme; and,

c) Document AJ, Fujihara et al. 2000, copied and confirmed blockade of NFκB signaling complexes *in vivo* in a lethal septic shock murine animal model of inflammation using importation competent peptide complexes.

2. For complexes formed between oligonucleotides and nucleic acids and importation competent peptides, the following examples of copying are relevant for *in vitro* uses: namely,

Documents AA, AB, AC and **AD** copy to confirm efficacy *in vitro* for peptide complexes formed between oligonucleotides or plasmids. The cellular functions effected by these complexes include: (a) blockade of cell division by antisense inhibition of cdc25 kinase (**Document AB**), (b) inhibition of HIV-1 reverse transcriptase (**Document AD**) and (c) inhibition of EGF-receptor signaling (**Document AF**).

3. A Medline search conducted on November 30, 2002 by Dr. Sundsmo, (see Declaration), recovered more than 150 citations relating to various uses of importation competent peptides for transduction of biologically active molecules, i.e., all published after 1994.

4. Several reviews of the contemporary art are provided herewith that identify the most exciting new opportunities for this technology: e.g.,

Document AL, Lindsay 2002, reviews peptide mediated cell delivery as follows: namely,

> "Interestingly, recent studies have identified several short peptide sequences named protein transduction domains (PTDs) or cell penetrating peptides (CPPs), which appear to rapidly translocate into all cells both in vitro and in vivo. Importantly, conjugation of proteins, peptides and antisense to these PTDs has been shown to deliver these cargoes effectively, allowing observation of biological action in several cell and animal models [1,2]. In this review, we examine the use of PTDs as a novel and potentially universal delivery system for delineation of protein function and target validation." (page 587, left column, Introduction section, lines 22-32).

Tabularized information in this document show more than 30 different intracellular targets effected in more than 40 different cell types (Table 1-2).

5. Document AI discloses the author's affiliation to be Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, NJ. 08543.

Applicants clearly recognized that they were first to recognize the broad future value of their discovery. Attempting to protect their invention from obvious and simple copying by others, the inventors indicated that:

> i) "The present invention relates generally to the delivery of biologically active molecules, such as peptides, polypeptides and nucleic acids, into the interior of cells. Specifically, the delivery is accomplished by administering to the cells a complex comprising the molecule linked to a signal peptide. Such delivery can be utilized for many purposes such as peptide therapy, antisense oligonucleotide therapy and gene transfer." (Field of the Invention, as filed in 1994); and,
>
> ii) "The present invention provides a method of importing a biologically active molecule into a cell *ex vivo* comprising administering to the cell, under import conditions, a complex comprising the molecule linked to an importation competent signal peptide, thereby importing the molecule into the cell. Molecules that can be delivered by this method can include, for example, peptides, polypeptides, proteins, nucleic acids, carbohydrates, lipids, glycolipids, and therapeutic agents." (Summary of the Invention, as filed in 1994).

Summary in Regards to the §112, First Paragraph Enablement Rejections :

The level of ordinary skill in the clinical arts delivering protein and peptides is high, as is the knowledge of those of skill in the gene therapy and molecular biology arts. Given the teaching in the specification, Applicants do not believe it would require undue experimentation for one of skill in the art to make and use the claimed invention, i.e., as is illustrated by at least Documents AA, AB, AC and AD (Appendix A and Supplement Information Disclosure Statement transmitted herewith).

It is not a requirement of §112 that an inventor completely reduce each and every aspect of every single different embodiment of the invention to practice prior to filing a patent application. Furthermore, it is unfair and unduly limiting to require applicant to limit claims to only specifically disclosed embodiments. To do so is contrary to the public policy upon which U.S. patent laws are based. In the instant case, disclosure by the inventors enables others to copy the invention by using a variety of other importation competent peptides to treat cells in a subject. Issuance of narrow claims in the instance application would result in a disclosure widely useful to potential infringers, a situation clearly unfavorable for the inventors, and this is clearly not fair. Because they were first to recognize the important uses of importation competent peptide complexes in human and animal therapy, and the requisite properties of the complexes so useful, Applicant's deserve broad claims.

Removal of the rejection is respectfully requested in view of the new claims, amendments and foregoing remarks.

Rejections Under 35 USC § 112, First Paragraph - Written Description:

Claims 6-15 stand rejected under 35 USC §112 as "failing to describe in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed had possession of the claimed invention."

The position of the Office in respect to Claims 6 and 11 is as follows: namely,

> "Claims 6 and 11 are drawn to a method of importing a biologically active molecule into a cell by linking the molecule to a importation competent signal peptide. The specification mentions SEQ ID NO. 5, the signal peptide from Kaposi fibroblast growth factor. This disclosure is not deemed to be descriptive of the complete structure of a representative number of species encompassed by the claims as one of skill in the art cannot envisage all importation competent signal peptides based on the teachings in the specification."

Respectfully, the skill in the art is high, it is not necessary for the specification to recite that which is obvious and direction provided in the specification, as filed, is sufficient for one skilled in the art to access a computer data base containing a listing of known hydrophobic signal sequences, thereby to identify useful sequences for testing according to the invention, and to identify an importation competent peptide as set forth in: for example,

> "Signal peptides can be selected, for example, from the SIGPEP database, which also lists the origin of the signal peptide.[30, 38] When a specific cell type is to be targeted, a signal peptide used by that cell type can be chosen. For example, signal peptides encoded by a particular oncogene can be selected for use in targeting cells in which the oncogene is expressed. Additionally, signal peptides endogenous to the cell type can be chosen for importing biologically active molecules into that cell type. And again, any selected signal peptide can be routinely tested for the ability to translocate across the cell membrane of any given cell type according to the teachings herein. Specifically, the signal peptide of choice can be conjugated to a biologically active molecule, e.g., a functional domain of a cellular protein or a reporter construct, and administered to a cell, and the cell is subsequently screened for the presence of the active molecule." (page , line of the specification as filed in 1994 and as set forth in the divisional filed in the year 2000).

Alternatively, one of ordinary skill in the art could, at the time the application was filed, access the published lists of signal peptide sequences as set forth in the cited #30 and #38 documents: namely,

> "30. von Heijne, *Protein Sequence Data Analysis* Vol. 1:41-42 (1987);
> 38. von Heijne and Abrahmsen, L., *FEBS Letters* 224:439-446 (1989)." (page , lines __ and __ of the specification).

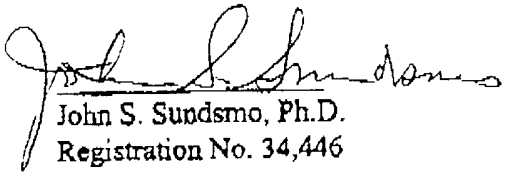
Conclusions

It is manifestly unfair to deny creative signet innovation access to the full measure of patent protection, i.e., rewarding those who come behind copying but not those who take the inventor's risks. While engaged in the past nine years of patent prosecution, those who have followed have adequately demonstrated the ease with which the claimed inventive methods may be copied.

If any issues remain which can be expeditiously addressed in teleconference, the Examiner is urged to contact Applicant's agent at 404-658-5249.

No additional fee is believed due; however, the Commissioner is hereby authorized to charge any deficiency or to credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted



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CERTIFICATE OF MAILING UNDER 37 C.F.R. § 1.8

I hereby certify that this correspondence, including any items indicated as being attached or enclosed, is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, Washington, D.C. 20231, on the date shown below.

Shari J. Corin

Shari J. Corin, Ph.D.

December 3, 2002
Date